REMARKS

Status of the Claims

Claims 1-31 are pending. Claims 23-31 were withdrawn from consideration by the Examiner. Claims 1-17 and 19-22 were rejected. Claim 18 was deemed allowable but objected to for depending from a rejected claim.

Response to the Advisory Action

In the Office Action of February 7, 2006, the Office rejected claims 1-4 and 7-9 under 35 U.S.C. § 102(b) as being anticipated by *Palomäki* (J. of Immunological Methods 145:55-63, 1991). The rejection was maintained in the Final Office Action of August 25, 2006. Applicants filed a response on December 22, 2006, but in the Advisory Action dated February 22, 2007, the Office maintained the rejection under 35 U.S.C. § 102, arguing that "Palmaki teaches the measurement of L1 plus L2 dependent measurements by taking absorbances at 450 nm (i.e. more than one reading), as recited in the alternative limitation of the instant claim 1." (Advisory Action, page 2 (emphasis added).) The Office alleges that *Palomäki* anticipates claim 1, which recites "determining an L1-dependent measurement signal at a different time from an L2-dependent measurement signal or an L1 plus L2-dependent measurement signal." (emphasis added.)

Applicants respectfully disagree with the Office's argument and respectfully suggest that the misunderstanding may be readily resolved. Specifically, Applicants disagree with the Office's assertion that *Palomäki* teaches more than one absorbance reading at 450 nm that allegedly serves to anticipate claim 1.

More specifically, claim 1 requires at least two separate measurements of a sample taken at different time points:

Measurement No. 1 measures an L1-dependent signal.

Measurement No. 2 measures an L2-dependent signal or an L1 plus L2-dependent signal. The "alternative limitation" of claim 1 as suggested by the Office refers to the alternative measurements of Measurement No. 2, but claim 1 still requires Measurement No. 1.

Palomäki teaches a method that involves a single measurement of absorbances at 450 nm (*Palomäki*, page 57, column 2 at ¶ 5.) ("The reaction was stopped by adding 100 µl of 1 N H_2SO_4 and absorbances at 450 nm were then measured using the Titertek Multiscan MCC/340 microtitre plate reader (Labsystems)") The fact that the word "absorbances" is in the plural form relates to the presence of multiple samples on the microtitre plate, whereby each sample is in a different well. (*Palomäki*, page 57, column 2 at ¶ 5.) ("Test samples and controls (50 µl) were added to the microtitre wells simultaneously with the HRP-Pab-HBsAg- and the HRP-Mab2-HBsAg-conjugates (50 µl)...") The plural form does not indicate that more than one measurement is taken for any individual sample.

Furthermore, *Palomäki* emphasizes the importance of using polyclonal and monoclonal HRP-coupled antibodies simultaneously (*Palomäki*, for example, page 55 at title and abstract; page 57, column 2 at ¶ 3; and page 62 at ¶ 4.) Moreover, the polyclonal and monoclonal antibodies are both labelled with the same horseradish peroxidase (HRP). (*Palomäki*, page 57, column 1 at ¶ 3.) Therefore, the single

absorbance measurement at 450nm captures the signals of both antibodies simultaneously.

In summary, the method described by *Palomäki* involves a single measurement of an individual sample that simultaneously measures the signals of the two HRP-labelled antibodies. Hence, when compared to the method of the instant invention, the measurement of *Palomäki* provides only one of the measurements required by the claim. Because claim 1 of the instant invention sets forth two separate measurements at different time points (i.e. Measurement No. 1 and No. 2), *Palomäki* does not describe, expressly or inherently, each and every element of claim 1. However, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. § 2131. Applicants therefore respectfully submit that *Palomäki* cannot anticipate claim 1 of the instant invention. Accordingly, withdrawal of the rejection is respectfully requested.

Office Action of February 7, 2006

In the Final Office Action of August 25, 2006, the Office maintained all rejections made in the prior Office Action of February 7, 2006. Accordingly, Applicants address the rejections issued in the Office Action of February 7, 2006.

35 U.S.C. § 102(b)

In addition to the response to the Advisory Action above, Applicants address the assertions presented by the Office in rejecting the claims under 35 U.S.C. § 102:

(1) In the Office Action dated February 7, 2006, the Office asserted that *Palomäki* "teaches a two one step EIA that a separate measurement was taken at optimal concentrations when the HRP-Pab-HbsAg was used alone or simultaneous with diluted HRP-Mab2-HbsAg in the assay (page 58, column 2, paragraph 2)." (Office Action, pages 3-4.) The recited paragraph of *Palomäki* reads as follows:

> "*Optimization of the HBsAg EIA*. The two one-step HBsAg EIA procedures showed similar sensitivity when the polyclonal enzyme tracer (HRP-Pab-HBsAg) at optimal concentration was used alone or simultaneously with the optimally diluted monoclonal enzyme tracer (HRP-Mab2-HBsAg); 0.6 and 0.3 ng/ml (standard procedure), 0.2 and 0.15 ng/ml (overnight procedure) for HBsAg/*ay* and HBsAg/*ad* subtypes, respectively (Fig.2). On the other hand, the sensitivity for subtype *ay* was only 3 ng/ml (standard procedure) and 0.4 ng/ml (overnight procedure) when the HRP-Mab2-HBsAg was used alone as the enzyme tracer." (*Palomäki*, page 58, column 2 at ¶ 2.)

Applicants respectfully submit that this paragraph does not describe any procedure that involves separate measurements of an individual sample. Rather, this paragraph describes the results of several separate EIA experiments that were carried out to optimize the conditions for the desired HBsAg EIA. The tested parameters included antibody type and antibody combination. These parameters were tested in two separate, one-step EIA procedures that used different incubation times (2 hrs or overnight). No more than one separate measurement appears to have been taken for any individual sample. Furthermore, the experimental conditions described in this paragraph did not eliminate the hook effect. However, the elimination of the hook effect is one of the main advantages of the instant invention.

(2) In the Office Action dated February 7, 2006, the Office asserted that "saturation of analyte A-binding sites of the binding partner R2 taking place at a higher analyte A concentration than that of R3 is inherent to the HBsAg assay" described by *Palomäki*, because the assay uses polyclonal (R2) and monoclonal (R3) antibodies as binding partners, and polyclonal antibodies inherently are "less specific" than monoclonal antibodies and "therefore would require more of the analyte to saturate its binding sites." (Office Action, page 4.) However, no authority for this assertion has been provided. Applicants respectfully disagree that polyclonal antibodies inherently require more analyte to saturate its binding sites than monoclonal antibodies. The Office's assertion is also contradicted by *Palomäki*, which suggested that the monoclonal antibody (R3) has a lower affinity to the commonly recognized HBsAg epitope than the polyclonal antibody (R2) (*Palomäki*, page 62, column 1 at ¶ 3.) ("...because of the lower affinity of the Mab2-HBsAg for the epitope also recognized by the Pab-HBsAg.") One skilled in the art would understand that the higher the affinity of an antibody for an antigen, the lower the concentration necessary for 50% of antigen to bind the antibody. Hence, in the particular antibody combination used by *Palomäki*, saturation of analyte A-binding sites of the binding partner R2 would take place at a lower analyte A concentration than that of R3, not at a higher concentration as asserted by the Office. Therefore, the use of polyclonal (R2) and monoclonal (R3) antibodies as binding partners does not make inherent that saturation of analyte A-binding sites of the binding partner R2 takes place at a higher analyte A concentration than that of R3.

Applicants respectfully note that a similar argument was found to be persuasive by the Office in the Office Action dated February 7, 2006, page 7 ("Applicant's

arguments filed October 31, 2005 have been fully considered and found to be persuasive:...Applicant contends that one skilled in the art would understand that the higher the affinity of an antibody for an antigen, i.e. the higher the affinity constant, then the lower the concentration of antigen necessary for 50% of antigen to bind to the antibody.").

(3) In the Office Action dated February 7, 2006, the Office asserted that *Palomäki* teaches a one-step or a two-step sandwich method. (Office Action, page 4.) ("The assay method can be a one or two step sandwich, (page 57, column 2, paragraph 4) which the examiner interprets as being heterogeneous or homogeneous.") Applicants respectfully disagree with this assertion. The cited paragraph discusses two different one-step EIA procedures but does not describe a two-step EIA procedure. (*Palomäki*, page 57, column 2 at ¶ 4.) ("Two one-step HBsAg EIA procedures were developed, differing only in their incubation times"). Indeed, *Palomäki* does not teach any two-step sandwich method. *Palomäki* simply explains the advantages of its one-step assay over "conventional two-step sandwich assays." Furthermore, Applicants note that the term "two-step sandwich assay" as used by *Palomäki* does not relate to the concept of separate measurements of an individual sample at different time points, as required by claim 1 of the instant application. Rather, the distinction between a one-step and a two-step sandwich assay relates to how the analyte is incubated with the capture antibody and the labelled antibody. (See, *Palomäki*, page 61, column 2 at ¶ 5.)

Accordingly, Applicants respectfully request withdrawal of the rejection.

35 U.S.C. § 103

In the Office Action of February 7, 2006, the Office issued rejections under 35 U.S.C. § 103, which were maintained in the Final Office Action of August 25, 2006. These include rejections of (1) claims 5, 6, and 19-22 over *Palomäki* in view of Marquardt et al. (U.S. Patent No. 6,610,494); (2) claims 10-15 over *Palomäki* in view of Cragle (U.S. Patent No. 4,590,169); and (3) claims 16-17 over *Palomäki* in view of Pitner et al. (U.S. Patent No. 5,641,629). Applicants respectfully disagree.

All of the rejected claims require the step of "determining an L1-dependent measurement signal at a different time from an L2-dependent measurement signal or an L1 plus L2-dependent measurement signal." (emphasis added.) As discussed in the response filed December 22, 2006, none of the secondary references make up for the deficiency of *Palomäki* discussed above. The Office stated in the Final Office Action on page 4 that it "relied on the teaching of Marquardt for the teaching of a member "XY" binding pair (i.e. biotin-avidin or avidin-streptavidin)." The Office also relied on Cragle "for its teaching of microparticles used as labels and considered to be a suspendable solid phase," and on Pitner "for its teaching of energy transfer assays." (Final Office Action of 8/25/2006 at page 5). However, none of these secondary references teach the step of "determining an L1-dependent measurement signal at a different time from an L2-dependent measurement signal or an L1 plus L2-dependent measurement signal." Therefore, Applicants respectfully request withdrawal of the rejections.

Conclusion

Applicants respectfully request that this Reply and Submission Under 37 C.F.R. § 1.114 be entered by the Office, placing claims 1-22 in condition for allowance. In view of the foregoing remarks, Applicants submit that this claimed invention is not anticipated or obvious. Applicants therefore request the entry of this Amendment, the Office's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Request for Interview

Should the Office maintain the rejections, Applicants request that the Examiner contact the undersigned at 650-849-6679 so that a suitable date and time can be scheduled for an Examiner interview to clarify the issues remaining in this case.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: July 20, 2007

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